REMARKS

Claims 1, 3-10, and 28-30, are pending in the present application. Withdrawn claims 2, and 11-27, have been cancelled without prejudice or disclaimer.

Claims 1, 3, 8-10, and 28, have been amended as requested by the Examiner, to italicize the terms "*Dunaliella*" and "*Dunaliella bardawil.*" No new matter has been added.

Applicants thank the Examiner for indicating that claims 9, 29, and 30 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 3 of the Official Action, claims 1, 8, and 28, have been rejected under 35 USC § 103(a) as being unpatentable over Kesharlal et al. in light of evidence readily admitted by Applicant.

The Examiner asserts that it would have been obvious to the skilled artisan to administer the composition taught by Kesharlal to provide the instantly claimed invention because at the time the invention was made it was well known in the art of medicine that anti-diabetic agents generally had the functional effect to reduce glucose levels in an individual afflicted with diabetes.

Applicants note that the Examiner has based this rejection on the abstract of the Kesharlal patent. Submitted herewith, please find a complete copy of the Kesharlal patent.

In view of the following, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all the claim limitations. *Amgen, Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. *See Ex parte Clapp*, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. *Id.* at 974.

The court in *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994), held that "A prior art reference may be said to *teach away* when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." The court in *Busch & Lamb, Inc. v. Barnes-Hind/Hydro curve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986), held that "A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered."

A brief analysis of Kesharlal is set forth below.

Kesharlal is directed to a process for the preparation of a synergistic composition for the treatment of diabetes, comprising carrot phytonutrients; natural carotenoids from *Dunaliella salina* or *marigold*; other antioxidants such as vitamin E, vitamin C; in association with other constituents such as chromium, zinc, selenium; and vitamins such as vitamin B1, B6, folic acid and vitamin B12. Kesharlal requires that the synergistic composition contain all of the foregoing components, for example, in order to prevent oxidative damage and supplement adequate nutrition.

It is submitted that a prima facie case of obviousness has not been established because Kesharlal does not teach or suggest all of the limitations of present claim 1. *See In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Present claims 8 and 28 are dependent on independent claim 1. Claims 1, 8, and 28, are method claims that require the administration of an effective amount of dried *Dunaliella* algae to a subject afflicted with diabetes and require a reduction in the subjects insulin and/or glucose plasma levels. Specifically, present claim 1 is directed to a method for reducing insulin and/or glucose plasma levels in a subject afflicted with diabetes, comprising administering to the subject an effective amount of dried *Dunaliella* algae, thereby reducing the subject's plasma insulin and/or glucose plasma levels.

Kesharlal does not teach or suggest the administration of ***dried Dunaliella algae***, let alone the administration of an effective amount of dried *Dunaliella* algae as required by present claims 1, 8, and 28. Rather, Kesharlal describes that *Dunaliella* is used as a 20 % dispersion of natural mixed carotenoids (see

page 14, last line), adsorbed on silicon dioxide and passed through a 40 mesh sieve (see the top of page 23). More specifically, the carotenoids are extracted from the *Dunaliella* to form a dispersion. Kesharlal does not teach how the extraction is carried out. In complete contrast to Kesharlal, the presently claimed dried *Dunaliella* algae is a crude powder that has not undergone any physical or chemical extraction or purification of carotenoids. The present specification at page 6, last paragraph, defines "dried *Dunaliella* algae" as a "crude *Dunaliella* algae" preparation. The preparation of "crude *Dunaliella* algae powder" is described on page 8 of the specification which states that *Dunaliella bardawil* was grown to obtain algae, the algae was harvested to obtain a paste, the paste was then washed and dried to yield crude *Dunaliella* algae powder.

In addition, Kesharlal does not teach or suggest a reduction in a subject's insulin and/or glucose plasma levels as required by present claims 1, 8, and 28. Kesharlal does not describe any experimental results that evidence that the synergistic composition is effective in treating diabetes, let alone evidence a reduction in a subject's insulin and/or glucose plasma levels. Moreover, none of the claims of Kesharlal relate to diabetes.

Further, Kesharlal does not teach or suggest the administration of ***only*** dried *Dunaliella* algae to a subject afflicted with diabetes. Rather, Kesharlal requires the administration of a ***synergistic composition*** of a number of components including the following: (1) carrot phytonutrients; (2) other carotenoids associated with micronutrients; (3) trace minerals; (4) natural caretenoids; and (5) other antioxidants. *See* Kesharlal at the paragraph bridging

pages 10 and 11, the paragraph bridging pages 11 and 12, page 12, lines 12-15, and claim 1. In contrast to Kesharlal, the presently claimed method requires the administration of ***only*** dried *Dunaliella* algae.

In fact Kesharlal ***teaches away*** from the administration of only dried *Dunaliella* algae to a subject afflicted with diabetes. Kesharlal describes, at page 14, lines 12-18, that supplementing with just one of the carotenoids, such as beta-carotene, can reduce levels of other carotenes in the body. Accordingly, Kesharlal *requires* the administration of an effective combination of carotenoids in order to benefit from the unique action of each carotenoid without adversely affecting the level of any individual carotenoid. *See* Kesharlal at page 5, lines 8-14.

In view of the foregoing, it is submitted that nothing in Kesharlal renders the subject matter of claims 1, 8, and 28, obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

II. At page 4 of the Official Action, claims 1, 8, 10, and 28, have been rejected under 35 USC § 103(a) as being unpatentable over Kesharlal in view of Takenaka and Tanaka.

The Examiner asserts that it would have been obvious to the skilled artisan to modify the method taught by Kesharlal by encapsulating the referenced composition as taught by Takenaka and Tanaka, to provide the instantly claimed method.

In view of the following, this rejection is respectfully traversed.

Applicants submit that Kesharlal does not teach or suggest the administration of an effective amount of ***dried Dunaliella algae*** to a subject afflicted with diabetes as required by the present claims. Kesharlal does not teach or suggest a reduction in a subject's insulin and/or glucose plasma levels as required by the present claims. Please see the analysis of Kesharlal set forth above.

Takenaka does not cure the deficiencies of Kesharlal because Takenaka also does not teach or suggest administering an effective amount of ***dried Dunaliella algae*** to a subject afflicted with diabetes, let alone a reduction in the subject's plasma insulin and/or glucose plasma levels, as recited in the present claims. Rather, Takenaka describes a preparation of a soft capsule for foods made from blending carotenoids extracted from algae with nutrients unstable to light and oxidation.

Tanaka does not cure the deficiencies of Kesharlal and Takenaka, taken alone or together, because Tanaka also does not teach or suggest administering an effective amount of ***dried Dunaliella algae*** to a subject afflicted with diabetes, let alone a reduction in the subject's plasma insulin and/or glucose plasma levels, as recited in the present claims. Rather, Takaka describes the preparation of a capsule for foods made from blending *Dunaliella* algae, cyclodextrin, an antioxidant, a lubricant and a binder, and encapsulating the mixture in a capsule.

In view of the foregoing, it is submitted that nothing in any of Kesharlal, Takenaka, and Tanaka, taken alone or together, render the claimed invention obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At page 6 of the Official Action, claims 1, 3-8, 10, and 28, have been rejected under 35 USC § 103(a) as being unpatentable over Kesharlal, Takenaka and Tanaka, in view of Beck, Pan, Heyman, and Smith.

The Examiner asserts that the combined teachings of Kesharlal, Takenaka, and Tanaka teach the instantly claimed invention except for wherein the crude Dunaliella powder is administered together with one or more activators of nuclear receptors. The Examiner asserts that it would have been obvious to the skilled artisan to add the instantly claimed ingredients to the method taught by the combined teachings of Kesharlal, Takenaka, and Tanaka, to provide the instantly claimed invention because the instantly claimed activators of nuclear receptors were known in the art for their beneficial functional effect for the treating diabetes, as evidenced by the teachings of Beck, Pan, Heyman, and Smith.

In view of the following, this rejection is respectively traversed.

An analysis of Kesharlal, Takenaka, and Tanaka, is set forth above. Again, none of Kesharlal, Takenaka, and Tanaka, taken alone or together, teach or suggest administering an effective amount of ***dried Dunaliella algae*** to a subject afflicted with diabetes, let alone teach or suggest a reduction in the subject's plasma insulin and/or glucose plasma levels, as presently claimed.

Likewise, none of Beck, Pan, Heyman, and Smith, taken alone or together, cure the deficiencies of Kesharlal, Takenaka, and Tanaka. Specifically, none of Beck, Pan, Heyman, and Smith, taken alone or together, teach or suggest administering an effective amount of ***dried Dunaliella algae*** to a subject afflicted with diabetes, let alone teach or suggest a reduction in the subject's plasma insulin and/or glucose plasma levels, as presently claimed.

Rather, Beck describes the use of bezafibrate for the treatment of normolipidaemic diabetes mellitus type II. Pan et al. describes a method for reducing the risk of Type II diabetes by administering a combination of: (1) a cholesterol lowering drug such as mevastatin, lovastatin, pravastatin or velostatin; and (2) an angiotensin converting enzyme inhibitor. Heyman describes methods and compositions for the treatment of non-insulin-dependent diabetes mellitus using an RXR agonist alone or in combination with a PPAR-γ agonist, e.g. a thiazolidinedione compound. Lastly, Smith describes a method for the treatment of diabetes mellitus comprising administering rosiglitazone and insulin.

In view of the above, it is submitted that nothing in Kesharlal, Takenaka, Tanaka, Beck, Pan, Heyman, and Smith, taken alone or in combination, renders the invention of claims 1, 3-8 and 28, obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

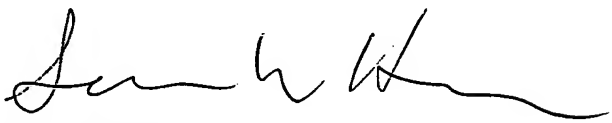
Conclusion

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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INDIAN PATENT SPECIFICATION

(51)	Int. Cl.	A 61 K 35/78 A 61 K 33/30, 33/04 C 07 D 307/62, 311/72, 415/00 C 07 H 23/00		(11)	Document No. 189624 IN
					Date of Document : 23-10-2001.
(52)	Ind. Cl:	55 E_4 32 G	A	(42)	Date of Publication: 29.03.03

(21)	Application No.:	1038 MUM 2001	(71)	Applicant: AJANTA PHARMA LIMITED AJANTA HOUSE, 98, GOVT. INDUSTRIAL AREA, CHARKOP, KANDIVLI (W), MUMBAI – 400 067. MAHARASHTRA, INDIA, AN INDIAN CO.
(22	Date of filing:	23-10-2001		
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	Claims:	08	(74)	Agent : BIYANI MILIND KESHARLAL
	Text : 30	Pages: Drgs NIL Sheet.		Examiner : D.B.K. SINGH

(54) Title : PROCESS FOR PREPARATION OF NOVEL COMPOSITION WITH CARROT PHYTONUTRIENTS FOR DIABETICS.

(57) Abstract: The Invention provides process of preparation of composition comprising, carrot phytonutrients; natural carotenoids from Dunaliella salina or marigold or the like, and/or combinations thereof; other antioxidants such as vitamin E, vitamin C; in association with other constituents such as chromium, trace elements like zinc, selenium; and vitamins such as, vitamin B1, Vitamin B6, folic acid and vitamin B12 for diabetics.

PRICE : THIRTY RUPEES

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

SECTION 10

The following Specification particularly describes the nature of this invention and the manner in which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to a process for preparation of unique synergistic composition comprising of carrot phytonutrients: natural carotenoids from Dunaliella salina or marigold or the like, and/or combinations thereof; other antioxidants such as vitamin E, vitamin C; in association with other constituents such as chromium, trace elements like zinc, selenium; and vitamins such as, vitamin B1, Vitamin B6, folic acid and vitamin B12 for diabetics.

More particularly it relates to a process for preparation of unique synergistic composition with better stability and shelf life by way of reducing the chances of degradation during the process of very sensitive oxidation prone ingredients like carrot phytonutrients; natural carotenoids from Dunaliella salina or marigold or the like; and other antioxidants such as vitamin E, vitamin C.

BACK GROUND OF THE INVENTION :

Diabetes is an endocrine and metabolic disorder, which is characterized by hyperglycemia of a defined degree and is linked with long term complications involving the eyes, kidneys, nerves, and blood vessels. It is ranked 7th among the leading causes of death. It has been rated 3rd when all its fatal complications are taken into account. Besides, diabetes is a leading cause of acquired blindness and accounts for 25% of cases, with end stage renal failure as well as 50 % of lower limb amputations.

Diabetes mellitus is a chronic disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or mounting resistance to its action. Clinically two types of diabetes mellitus are identified. "Type I or insulin Dependent Diabetes mellitus (IDDM)" where for controlling diabetes the patient requires daily injections of insulin. Another type is recognized clinically as "Type II or Non-Insulin Dependent Diabetes Mellitus (NIDDM)" in which patients are not insulin dependent or ketosis-prone, although they may use insulin for correction of symptomatic or persistent hyperglycemia.

There are about 175 million diabetics world over. The tremendous economic and physical toll diabetes extracts from society is, in large part, secondary to both the short and long term complications of the disease. It is estimated that a diabetic patients life is shortened by 10 to 15 years, and those years of life are marked by a health care tab 4 times that of a non-diabetic patient.

The thrust in recent years has been to introduce or develop drugs for example metformin, troglitazone, etc. which act directly to reduce insulin resistance, that is insulin sensitizers or enhancers. These drugs alone cannot address the secondary complications associated with oxidative damage and lack of adequate nutrition. Hence there is a need for a composition which can prevent the oxidative damage, supplement the nutritional requirement and at the same time be effective in diabetes control. The present invention provides such a composition containing carrot phytonutrients antioxidant carotenoids and

vitamins, vital minerals like chromium, zinc, selenium and vitamins which prevents oxidative damage. supplements adequate nutrition and provides insulin resistance.

It has been reported that free radical oxidative stress has been implicated in the pathogenesis of a variety of human diseases. Natural antioxidant defenses have been found to be defective in many of the same diseases. This has lead to the suggestions that oxidative damage and therefore disease progression may be retarded by supplementing natural antioxidant defenses. Potential antioxidant therapy includes natural antioxidant enzymes and vitamins or synthetic agents with antioxidant activity. Diseases where antioxidant therapy may be beneficial include diabetes mellitus

Though not linked directly role of antioxidants such as vitamin E, vitamin C, carotenoids can also be linked with diabetes. Free radicals are produced in the body as byproducts of normal metabolism and as a result of exposure to radiation and some environmental pollutants. Because they are highly reactive, they can damage cellular components and are implicated in a variety of diseases. Free radical are normally neutralized by efficient systems in the body that include the antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and the nutrient derived antioxidant small molecules (such as vitamin E, vitamin C, carotenes etc.). In healthy individuals, a delicate balance exists between free radicals and antioxidants. In some pathologic condition such as diabetes and critically ill patients, oxidative stress causes the levels of antioxidants to fall below normal. Antioxidant supplements for such condition are expected to be of benefit.

Moreover the preferred composition includes carrot phytonutrient obtained as per the process described in our US patent 6056962, consisting of natural carotenoids in association with other micronutrients including trace minerals, mimicking the form in which they are naturally available. Trace minerals as present in the carrot extract are beneficial in ameliorating physiological deficiencies associated with diabetes. Hence it provides a synergistic, bioavailable form of natural carotenoids, with micronutrients. Further the composition consists of natural carotenoids from Dunaliella salina or marigold or the like and/or combinations thereof. With respect to the carotenes, the clinical results show that they function most effectively when used together in an united effort. Research has shown that by supplementing with just one of the carotenoids, such as beta-carotene, levels of other carotenes in the body may actually be reduced. Hence the present invention provides an effective combination of carotenoids, in order to benefit from the unique action of each carotenoid without adversely affecting the level of any individual carotenoid.

There are many clinical studies which have reported the role of chromium, vitamins and trace elements and their supplementation in diabetes.

Diabetes mellitus is a chronic metabolic disorder which can alter the nutritional status of the individual. Some micronutrients, in particular zinc and chromium, have been implicated in the pathogenesis of carbohydrate intolerance.

Chromium is reported to be an essential nutrient involved in the metabolism of glucose, insulin and blood lipids. Sub-optimal dietary intake of chromium is associated with increase risk factors associated with diabetes and cardiovascular diseases. Chromium increases insulin binding to cells, insulin receptor number and activates insulin receptor kinase leading to increased insulin.

It has also been indicated that chromium functions in maintaining normal glucose tolerance primarily by regulating insulin action. In the presence of optimal amount of biologically active chromium, much lower amounts of insulin are required. Glucose intolerance, insufficient to dietary chromium appears to be wide spread. Improved chromium nutrition leads to improved sugar metabolism in diabetics.

Chromium is an essential element required for normal carbohydrate and lipid metabolism. Insufficient dietary chromium has been linked to maturity –onset diabetes and cardiovascular diseases. The dietary chromium intake of most individuals is considerably less than the suggested safe and adequate intake. Supplementation of chromium to normal free living individuals often leads to significant improvements in glucose tolerance, serum lipids including high density cholesterol, insulin, and insulin binding. Chromium also tends to normalize blood sugar. Chromium supplementation of subjects with alleviated blood sugar following a glucose load, leads to a decrease in blood sugars, while hypoglycemics responds to supplemental chromium by an increase in hypoglycemic glucose values, increased insulin binding and alleviation of hypoglycemic symptoms. In summary dietary intake of chromium is suboptimal and this

is exacerbated by increased chromium losses due to stress and certain refined foods including simple sugars that enhance chromium losses. Supplemental chromium is associated with improvements of risk factors, associated with maturity-onset diabetes.

There is accumulating evidence that the metabolism of several trace elements is altered in insulin-dependent diabetes mellitus and that these nutrients might have specific roles in the pathogenesis and progress of this disease. Increased urinary loss of zinc is a commonly encountered feature of diabetes. Chromium increases tissue sensitivity to insulin and tends to raise high-density lipoprotein (HDL) cholesterol and the HDL:low-density lipoprotein ratio. Selenium is involved in processes which protect the cell against oxidative damage by peroxidase produced from lipid metabolism. Appropriate trace element supplementation might prove beneficial in ameliorating some physiological deficiencies associated with diabetes and prevent or retard secondary complications.

Some studies have discussed the plasma vitamin levels in association with human diabetic condition. Plasma vitamin B1 level of diabetic patients is revealed in the state of marginal deficiency. Vitamin B6, as the coenzyme pyridoxal phosphate, plays an important role in the metabolism of carbohydrates, therefore B6 has been associated with impairments in gluconeogenesis and abnormal glucose tolerance. Vascular complications of diabetes mellitus, such as atherosclerosis and retinopathy are considered to be related with glycation of low density lipoprotein which induces oxidative injuries to vascular endothelium. Administration of vitamins to diabetic patients reduces insulin requirement and attracts much attention for improvement of vascular complications. Vitamins

function not only as nutritional supplements for deficiency, but pharmacological agents for treatment.

In view of the role of antioxidants in preventing free radical oxidative damage and association of carotenoids. chromium, trace elements, vitamins, in diabetes as indicated by the above studies the present invention provides an unique synergistic composition comprising of carrot phytonutrients consisting of bio-available form of natural beta-carotene, other carotenoids associated with micronutrients and trace minerals in combination with chromium, vitamins and trace elements for diabetics.

Since the novel synergistic composition of the present invention comprises of very sensitive and oxidation prone ingredients like carrot phytonutrients, which comprises of natural beta-carotene and other carotenoids; natural carotenoids from Dunaliella salina or marigold or the like, there has been provided in accordance with the present invention a process for preparation by reducing the chances of degradation during the process of the said very sensitive and oxidation prone ingredients for providing better stability and shelf life to the composition for diabetics.

PRIOR ART

United States patent 5614224 (1997) relates to a daily nutritional supplement and method of administering it to assist in the metabolism of glucose. The supplement includes sources of vanadate and chromium as well as L-carnitine.

United States Patent 5,730,988 (1998) describes nutritional supplements and methods for administering nutritional supplements that improve glucose metabolism, particularly for persons with diabetes. A first nutritional supplement or phase I supplement comprises a source of chromium. A second nutritional supplement or phase II supplement comprises Gymnema sylvestre and lipoic acid.

United States Patent 5,962,030 (1999) discloses a nutritional supplement and method of administering it to assist in the metabolism of glucose for patients with diabetes and pre-diabetes. The supplement preferably includes anchor components of Chromium Polynicotinate and Picolinate, Vanadyl Sulfate, Vitamin E Natural, Standardised Willow Bark (aspirin), and Magnesium Chloride, Citrate, Fumarate, Malate, Glutorate, and Succinate Complex, Folic Acid, and Alpha-Lipoic Acid.

The afore mentioned prior arts discloses the supplements for improvement of glucose metabolism comprising of chromium, vitamins, trace elements, or enzymes, etc. The prior art compositions consist of either Vitamin – A or synthetic beta-carotene, where as the present invention composition includes carrot phytonutrients derived as per the process described in our US patent 6056962 dated May 2, 2000, consisting of natural beta carotene and other carotenoids in association with micro-nutrients including trace minerals and vitamins as are naturally present in carrots. In pathologic condition such as diabetes, natural antioxidant defenses have been found to be defective and oxidative stress causes the levels of antioxidants to fall below normal. Hence present invention composition having carrot phytonutrients provides an antioxidant supplement providing

natural antioxidant defenses as well as retarding oxidative damage and therefore disease progression, reducing chances of secondary complication associated with diabetes. Also the trace minerals as present in the carrot extract are beneficial in ameliorating physiological deficiencies associated with diabetes.

Thus the present invention composition comprising of carrot phytonutrients with bio-available form of natural beta-carotene, vitamins, and trace minerals; other antioxidants like vitamin E and C, vital minerals like chromium, zinc, selenium and vitamins like vitamin B1, B6, folic acid and vitamin B12 provides a synergistic and unique therapy for diabetics unlike the compositions of prior arts.

Moreover the prior arts provides the compositions without assuring means to protect the sensitive ingredients contained therein during the process of formulating or otherwise, which could provide the stability to the composition. Whereas unlike prior arts the present invention provides a process which reduces the chances of degradation during the process of the very sensitive and oxidation prone carotenoids, other antioxidants, vitamins contained therein to provide the better stability and shelf life to the composition for diabetics.

OBJECT OF THE INVENTION

The main object of the present invention is to provide a process for preparation of unique synergistic composition for diabetics comprising of carrot phytonutrients consisting of natural beta-carotene, other carotenoids associated with micronutrients and trace

minerals; natural carotenoids from Dunaliella salina or marigold or the like. and/or combinations thereof ; other antioxidants viz. vitamin E, vitamin C, vital elements such as chromium, zinc. selenium; and vitamins such as. vitamin B1, Vitamin B6. folic acid and vitamin B12.

Another aspect of the present invention is to provide a process for preparation of synergistic composition comprising of very sensitive and oxidation prone ingredients like carrot phytonutrients obtained as per the process described in our US patent 6056962 with bio-available form of natural beta-carotene; and other carotenoids vitamins. and trace minerals; natural carotenoids from Dunaliella salina or marigold or the like.

Yet another aspect of the present invention is to provide a process for preparation of novel synergistic composition for diabetics with better stability and shelf life by reducing the chances of degradation of very sensitive and oxidation prone ingredients like carrot phytonutirents comprising of beta-carotene, other carotenoids; other natural carotenoids from Dunaliella salina or marigold or the like, other antioxidants contained therein during the process.

SUMMARY OF THE INVENTION

The present invention provides a process for preparation of novel synergistic composition for diabetics. A preferred composition includes carrot phytonutrients consisting of natural beta-carotene. other carotenoids associated with micronutrients and trace minerals: natural carotenoids from Dunaliella salina or marigold or the like. and/or

combinations thereof, other antioxidants such as vitamin E, vitamin C, an effective amount of vital mineral elements like chromium, zinc, selenium and vitamins like vitamin B1, Vitamin B6, folic acid and vitamin B12. Since the composition includes carotenoids such as those from carrot phytonutrients comprising of beta-carotene with other carotenoids; other natural carotenoids from the sources like Dunaliella salina, marigold or the like which are very sensitive and oxidation prone, there has been provided a process to minimize the chances of degradation of the said sensitive ingredients to increse the stability and shelf life of the composition.

DETAILED DESCRIPTION

The present invention provides a process for preparation of unique synergistic composition comprising of carrot phytonutrients (obtained as per the process described in our US patent 6056962, dated May 2, 2000); antioxidants, mineral and vitamin for diabetics. The synergistic composition prepared in accordance with the present invention not only enhances the glucose metabolism in diabetic patients but also may be used by individuals with no apparent symptoms of diabetes, the composition could also be used by individuals with maturity onset diabetes to prevent, reduce the necessity of other anti-diabetic medications. Moreover the composition has ingredients which can also work together with insulin to enhance its effect on the regulation of glucose concentration in the blood by improving metabolism of glucose.

The process of the present invention has been so provided so as to reduce the chances of the degradation of the very sensitive ingredients like beta-carotene and other carotenoids

contained in carrot phytonutrients: other natural carotenoids from Dunaliella salina, marigold; or other antioxidants during the formulation and thereby improving the stability and shelf life of the composition without lose of any of the desirable attributes of the any of the ingredients to achieve the therapeutic effect.

The composition of the present invention containing carrot phytonutrients with naturally available beta-Carotene, other carotenoids, micronutrients and trace minerals; natural carotenoids from Dunaliella salina or marigold or the like, and/or combinations thereof, other antioxidants such as vitamin E, vitamin C, in combination with effective amounts of metabolically available forms of chromium; other trace elements such as zinc and selenium; and vitamins such as vitamin B1, B6, folic acid and B12. These components of the present composition perform different functions, which when administered in appropriate dosage form in combination, work together synergistically to enhance effect of one another thereby providing a better activity. The role and dosage of the each of the component of the present invention is set forth below, followed by process of preparation to ensure stability and shelf life of the composition.

Antioxidants are compounds which react readily with oxygen, the ease of this reaction enables them to react with the free radical generators, and quench free radical production. A free radical is an incomplete highly reactive molecule capable of destroying an enzyme, protein, genetic material or even an entire cell over time. The free radical usually generates a chain of free radical reactions resulting in thousands of free radicals being released to destroy the cell components. This process is known as biological

magnification. The antioxidant not only help protect the body against the destructive effects of these free radicals. but also stimulate the immune response to help fight existing disease, and they tend to normalize the balance of hormone-like chemicals in the body. The antioxidants therefore protect and repair cellular tissue from this free radical damage. Some important antioxidants are vitamin E. vitamin C, niacin, carotenoids etc.

The present invention composition contains carrot phytonutrients which contains carotenoids in association with other micronutrients including trace minerals, in the form in which they are naturally available. Trace minerals of carrot phytonutrients are beneficial in ameliorating physiological deficiencies associated with diabetes. Hence carrot phytonutrients provide a synergistic, bio-available form of natural carotenoids, with micronutrients. Further the composition consists of natural carotenoids from Dunaliella salina or marigold or the like and/or combinations thereof. With respect to the carotene, the clinical results show that they function most effectively when used together in an united effort. Research has shown that by supplementing with just one of the carotenoids, such as beta-Carotene. levels of other carotenes in the body may actually be reduced. Hence the present invention provides an effective combination of carotenoids, in order to benefit from the unique action of each carotenoid without adversely affecting the level of any individual carotenoid. Moreover natural carotenoids which are pro-vitamin A also acts as a source of vitamin A necessary to the utilization of protein and beneficial to the metabolism of glucose. The present invention composition contains carrot phytonutrients in the range of 10 mg to 1000 mg preferably in the range of 50 mg to 500 mg. natural mixed carotenoids from Dunaleilla salina in the from of 20 %

dispersion in the range of 1 mg to 100 mg preferably in the range of 5 mg to 25 mg, natural carotenoids from marigold in the from of 7.5 % dispersion in the range of 10 mg to 1000 mg preferably in the range of 50 mg to 500 mg.

Vitamin E is the most widely studied of the antioxidant vitamins. The interest in vitamin E as an antioxidant is based on the many demonstrations in humans that giving vitamin E as a supplement decreases the oxidation of low -density lipoprotein (LDL) ex vivo, an event critical in the atherogenic process. The primary role of vitamin E is the prevention of oxidation of polyunsaturated fatty acids. Vitamin E reacts with free radicals, which are the cause of oxidative damage to cell membranes, without the formation of another free radical in the process. Another unrelated benefit of vitamin E supplementation is the favorable effect it has on insulin sensitivity, glucose metabolism and lipid levels in both healthy subjects and patients with type II diabetes. The present invention composition contains vitamin E in the range of 3 mg to 200 mg preferably in the range of 10 mg to 100 mg.

Vitamin C, also called ascorbic acid, is a powerful water-soluble antioxidant that is vital for the growth and maintenance of all body tissues. Vitamin C helps regulate blood pressure, contributes to reduced cholesterol levels, and aids in the removal of cholesterol deposits from arterial walls, thus preventing atherosclerosis. Diabetics tend to have low levels of vitamin C not only in the plasma but also in the white blood cells, which constitute our immune defenses. One study, conducted at the University of Massachusetts, measured the ascorbic acid content of mononuclear leukocytes in adults

with insulin-dependent diabetes mellitus. This content level, which serves as a gauge of the vitamin C status of tissues, was reduced by 33% in diabetic patients, even though their intake of dietary vitamin C was adequate. According to the researchers, this impaired storage capacity "supports the theory that intercellular scurvy contributes to the chronic degenerative complications of the disease.". (J. J. Cunningham et al., "Reduced Mononuclear Leukocyte Ascorbic Acid Content in Adults with Insulin-Dependent Diabetes Consuming Adequate Dietary Vitamin C:" Metabolism; February 1991; 40(2); p. 146-9). The present invention composition contains vitamin C in the range of, 25 mg to 250 mg preferably in the range of 100 mg to 200 mg.

Chromium possesses properties, which both mimic and enhance effect of insulin. Many clinical studies have shown that chromium plays a role in both metabolism of glucose and action of insulin in the human body. The composition of the present invention contains chromium in the form of salts, such as chromium picolinate, chromium polynicotinate, chromium chloride, chromium-niacin complex or the like. The present invention composition contains chromium in the range of 50 to 1000 mcg, preferably in the range of 100 to 500 mcg.

Zinc is found in all cells in the body and is an integral component of over 200 enzymes, moreover zinc is abundant in the bone, kidneys, liver, pancreas and the retina. It plays a major role in supporting the immune system, interacts in the antioxidant metabolism. In the present invention composition zinc is incorporated in salt form. Such as zinc sulphate, zinc sulphate monohydrate, zinc gluconate or the like. The present invention

composition contains zinc in the range of 7 to 90 mg, preferably in the range of 10 to 45 mg.

Selenium is an essential trace element and is an integral part of the enzyme system glutathione peroxidase; this enzyme protects intracellular structures against oxidative damage. In the present invention composition selenium is incorporated in salt form, such as selenium dioxide monohydrate, selenium methionine, or the like. The present invention composition contains selenium in the range of 31.5 to 400 mcg, preferably in the range of 50 to 200 mcg.

Vitamins that are particularly beneficial to the metabolism of glucose are the B- vitamins and vitamin A. The B vitamins contained within the present invention are B1, B6 and B12. The B- vitamins are required resources for the operation of the nervous system and the adrenal glands. Adrenal glands products are found to be responsible for primary defense mechanism of the immune system against stress. Adrenal glands secrete hormones directly into the bloodstream. Each gland is divided into two parts, namely, an inner medulla and an outer cortex. The medulla section produces two types of hormones and takes all of its cellular instructions from the nervous system. The cortex produces and secretes the hormones called corticosteroids, which affect the way foods are stored, processed and used inside the body. The adrenal glands also have a direct linkage to healing mechanism inside the body, and strengthen the response and function of the immune system.

Vitamin B1 is also referred as thiamin. It is necessary for proper nervous system function. It is known to help formation of blood cells and necessary for proper nervous system function. It also helps to maintain smooth muscle and helps keep collagen-rich connective and mucous membranes healthy. The present invention composition contains vitamin B1 in the range of, 0.9 to 300 mg preferably in the range of 5 to 100 mg..

Vitamin B6 commonly referred as pyridoxine. is involved principally in amino acid metabolism, but is also involved in carbohydrate and fat metabolism. The present invention composition contains vitamin B6 in the range of, 1.5 to 400 mg preferably in the range of 3 to 100 mg.

Folic acid is another B vitamin used is the present invention. It is essential in the production of red blood cells. the production of hormones and synthesis of DNA. The present invention composition contains folic acid in the range of, 0.2 mg to 15 mg preferably in the range of 1 mg to 10 mg.

Vitamin B12 is commonly referred as cyanocobalmin. It is necessary for overall metabolism and nervous system function. The present invention composition contains vitamin B12 in the range of. 1 mcg to 1000 mcg preferably in the range of 10 mcg to 100 mcg.

Apart from the afore mentioned ingredients the composition also comprises of other pharmaceutically inert excipients like diluents. protective colloids, lubricants. or the like.

In the present invention process. typically the diluent is at least one, selected from starch, microcrystalline cellulose. dicalcium phosphate, tricalcium phosphate. calcium silicate. maltodextrin. or the like or the combination thereof, which could be used in the range of 5% to 60% preferably 10% to 40% by weight of the composition.

In the present invention process, typically the protective colloid is at least one. selected from gelatin, starch. gum acacia. dextrins or starch derivatives and/or combinations thereof. The protective colloids are used in the range of 1% to 40% preferably 5% to 20% by weight of the composition.

In the present invention process. typically the lubricant is at least one, selected from talc, magnesium stearate. colloidal silicon dioxide. stearic acid, or the like and or combination thereof. The lubricants are used in the range of 0.5 % to 10% preferably 1% to 5% by weight of the composition.

The synergistic composition of the present invention can be formulated in a suitable pharmaceutical oral dosage form like tablets. dispersible tablets. chewable tablets, capsules, powder or granules filled in sachet packs or the like.

The present invention composition was formulated into tablet form, since during tablet compression the granules are compacted together reducing effective surface area at the same time removing air to a large extent. thus minimising exposure to air and reducing

chances of oxidation thereby increasing the stability / shelf life of the tablet dosage form. Whereas in the capsules the granules are free flowing with presence of intragranular air and headspace in the capsule, which increases the susceptibility to oxidation thereby affecting the stability. Hence for the present invention tablets were selected as the dosage form of choice.

The present invention composition was prepared in accordance with process described herein. The process comprises of:

Part 1:

a) blending carrot phytonutrients with suitable diluent along with folic acid, pyridoxine hydrochloride, cyanocobalamin and passing through 40 BSS sieve,

b) adsorbing the Dunaliella salina carotenoids dispersion and the marigold extract on adsorbent and passing through. 40 BSS sieve,

c) mixing the carotenoids mixture with the carrot phytonutrients blend,

d) granulating the resultant blend with a solution of gum acacia,

e) drying the granules in a vacuum drier at a temperature not exceeding 55 °C and passing the dried granules through 16 BSS sieve,

Part 2 :

f) mixing the mineral salts of the composition like zinc sulfate with the diluent vitamin C,

g) dissolving the selenium salts in water and adsorbing on the vitamin E Acetate powder and passing the blend through 40 BSS sieve,

h) dissolving the chromium salts in water or mixing dry by geometric dilution with the vitamin E Acetate powder and passing the blend through 40 BSS sieve,

i) mixing the vitamin E acetate blend with the zinc sulfate blend,

j) drying the granules in a fluid bed drier at a temperature not exceeding 55 °C and passing the dried granules through 16 BSS sieve,

Part 3:

k) mixing the dried granules of part 1 and 2

l) lubricating the dried and mixed granules with lubricant, followed by addition of crosscarmellose sodium followed by compression into tablets using suitable dies and punches.

m) coating the tablets with hydroxy propyl methyl cellulose, propylene glycol and a blend of titanium dioxide/Iron oxide red in a conventional way, in a coating pan.

The process was carried out in such a way so as to avoid interactions between ingredients namely the carotenoids and vitamins with the minerals. The process conditions were selected to ensure the stability of the carotenoids. Care was taken during the process to minimize exposure to air, heat and light to avoid the degradation of the carotenoids. All the steps of process were carried out in diffused light to avoid oxidation of light sensitive carotenoids present in carrot phytonutrients, other natural carotenoids from Dunaliella salina and marigold.

Also to protect the degradation prone carotenoids, other antioxidants and vitamins from exposure of air, all the in-process material was stored in 40 micron aluminum foil pack, either vacuum sealed or pressed to remove all air from the pack.

Also care was taken during the process to prevent the degradation of heat sensitive carotenoids and antioxidants by carrying out all the drying operations below 60° C temperature

The following examples illustrate but do not limit the scope of the invention. It should be understood that various changes and modifications will be apparent to those skilled in the art. However such changes and modifications of the present invention can be made without departing from its spirit and scope and without diminishing its attendant advantages.

EXAMPLES

Example 1 :

Part 1 :

The carotenoids and Micronutrients of carrots (100 mg), folic acid (1500 mcg), pyridoxine hydrochloride (3 mg), and cyanocobalmin (15 mcg) were passed through 40 mesh British standard sieve individually and loaded in the mass mixer and mixed for 5 minutes. The thiamin mononitrate (10 mg), and microcrystalline cellulose (36.25 mg) were mixed together and passed through 60 mesh British standard sieve and loaded in the

mass mixer. The natural mixed carotenoids from Dunaliella salina as 20% dispersion (13.5 mg) and marigold extract as 7.5 % dispersion (12 mg) were weighed together and mixed. The mixture was adsorbed on silicon dioxide (27 mg) and passed through 40 mesh standard British sieve. This mixture was then loaded in the mass mixer and mixed for 5 minutes. The gum acacia (31 mg) was dissolved in water and the material in the mass mixer was granulated with the gum acacia solution. The granules were dried in a vacuum drier at a temperature of 50°C to 55°C. The dried granules were sifted through 16 British standard sieve.

Part 2:

The vitamin C (150 mg) was passed through 40 British standard sieve and loaded in the mass mixer. The zinc sulfate (70 mg) and microcrystalline cellulose (34.37 mg) were mixed together and passed through 60 British standard sieve and added to the vitamin C in the mass mixer and mixed for 5 minutes. The vitamin E acetate (25 mg) was mixed with the silicon dioxide (25 mg) and passed through 40 British standard sieve. The selenium dioxide (25 mg) and chromium chloride (1.02 mg equivalent to 200 mcg of chromium) were dissolved in water and adsorbed on the vitamin E acetate powder. The mixture was then passed through 40 British standard sieve. The starch gelatin paste were prepared by dissolving starch (11.7 mg) and gelatin (5.0 mg) in the water and the mixture in the mass mixer was granulated with this paste. The granules were dried in the fluid bed dryer at a temperature of 50°C to 55°C. The dried granules were sifted through 16 British standard sieve.

Part 3:

The lubricants talc (7.2 mg), magnesium stearate (3.6 mg), colloidal silicon dioxide (7.2 mg), crosscarmellose sodium (28.8 mg), microcrystalline cellulose (164.54 mg) were mixed together and passed through 60 British standard sieve. Granules of part 1 and 2 were mixed together and lubricated with the lubricants. The lubricated granules were compressed on 12.7 mm standard concave punches.

Coating:

Hydroxypropyl methyl cellulose (17.69 mg), titanium dioxide (5.78 mg), red oxide of Iron (1.06 mg), were dissolved in methylene chloride and stirred for 10 minutes, isopropyl alcohol (0.16 ml), followed by propylene glycol (3.59 mg) were added and stirring was further continued for 45 minutes. The resultant mixture was then filtered through 200 mesh British standard sieve and the tablets were coated with this solution in a conventional way in a coating pan.

Example 2 :

Part 1 :

The carotenoids and Micronutrients of carrots (100 mg), folic acid (1500 mcg), pyridoxine hydrochloride (3 mg), and cyanocobalmin (15 mcg) were passed through 40 mesh British standard sieve individually and loaded in the mass mixer and mixed for 5 minutes. The thiamin mononitrate (10 mg), and microcrystalline cellulose (36.25 mg) were mixed together and passed through 60 mesh British standard sieve and loaded in the mass mixer. The natural mixed carotenoids from Dunaliella salina as 20% dispersion (13.5 mg) and marigold extract as 7.5 % dispersion (12 mg) were weighed together and

mixed. The mixture was adsorbed on silicon dioxide (27 mg) and passed through 40 mesh standard British sieve. This mixture was then loaded in the mass mixer and mixed for 5 minutes. The gum acacia (31 mg) was dissolved in water and the material in the mass mixer was granulated with the gum acacia solution. The granules were dried in a vacuum drier at a temperature of 50°C to 55°C. The dried granules were sifted through 16 British standard sieve.

Part 2:

The vitamin C (150 mg) was passed through 40 British standard sieve and loaded in the mass mixer. The zinc sulfate (70 mg) and microcrystalline cellulose (34.37 mg) were mixed together and passed through 60 British standard sieve and added to the vitamin C in the mass mixer and mixed for 5 minutes. The vitamin E acetate (25 mg) was mixed with the silicon dioxide (25 mg) and passed through 40 British standard sieve. The selenium dioxide (25 mg) was dissolved in water and adsorbed on the vitamin E acetate powder. The mixture was then passed through 40 British standard sieve. The chromium picolinate (1.61 mg equivalent to 200 mcg of chromium) was mixed with above resultant powder. The starch gelatin paste was prepared by dissolving starch (11.7 mg) and gelatin (5.0 mg) in the water and the mixture in the mass mixer was granulated with this paste. The granules were dried in the fluid bed dryer at a temperature of 50°C to 55°C. The dried granules were sifted through 16 British standard sieve.

Part 3:

The lubricants talc (7.2 mg), magnesium stearate (3.6 mg), colloidal silicon dioxide (7.2 mg), microcrystalline cellulose (164.54 mg) followed by addition of crosscarmellose sodium (28.8 mg), were mixed together and passed through 60 British standard sieve. Granules of part 1 and 2 were mixed together and lubricated with the lubricants. The lubricated granules were compressed on 12.7 mm standard concave punches.

We claim,

1. A process for preparation of unique synergistic composition of carrot phytonutrients and other natural carotenoids derived from source like Dunaliella salina, or marigold or the like and/or combination thereof, in combination with chromium in oral dosage form for diabetics; further comprising of other antioxidants like vitamin E, vitamin C or the like; trace elements like zinc, selenium, or the like; vitamins like, vitamin B1, vitamin B6, Folic acid, vitamin B12, or the like in therapeutic range and other pharmaceutically accepted inert excipients, which comprises the steps of :

a. preparing active granule A - by blending carrot phytonutrients with folic acid, pyridoxine hydrochloride, cyanocobalamin, and thiamin mononitrate using appropriate diluent; adsorbing the other natural carotenoids dispersion on suitable adsorbent; mixing adsorbed carotenoids with blend of carrot phytonutrients and vitamins; granulating the resultant blend and drying ,

b. preparing active granule B – by adsorbing selenium salt and chromium salt solution separately on vitamin E powder or Vitamin E adsorbate prepared by adsorbing vitamin E acetate oil on suitable adsorbent and sifting; mixing the resultant blend with zinc salt and Vitamin C, followed by granulating; drying and sieving of the resultant granules.

c. mixing the active granules A and B, lubricating and drying, compressing the dried lubricated granules into tablets using suitable dies and punches, followed by film coating in a conventional way, in a coating pan,

wherein, all the process steps are carried out in diffused light, relative humidity not exceeding 50%, temperature not exceeding 25 ° C (except drying), drying operations carried at temperature not exceeding 50° C, all steps carried out in succession

immediately one following the other without any gap in-between, and keeping the exposure to air minimum throughout for avoiding degradation of sensitive materials and thereby improving stability.

2. A process for the preparation of synergistic composition as claimed in claim 1 wherein active ingredients are present in the said therapeutic range of ,

a. 10 mg to 1000 mg, preferably 50 mg to 500 mg, of carrot phytonutrient,

b. 1 mg to 100 mg, preferably 5 mg to 25 mg, of natural carotenoids from Dunaliella salina,

c. 10 mg to 1000 mg preferably 50 mg to 5000mg of natural carotenoids from marigold,

d. 3 mg to 200 mg, preferably 10 mg to 100 mg of vitamin E,

e. 25 mg to 250 mg, preferably 100 mg to 200 mg, of vitamin C,

f. 50 mg to 1000 mcg, preferably 100 mcg to 500 mcg, of chromium,

g. 7 mg to 90 mg, preferably 10 mg to 45 mg of zinc,

h. 31.5 mcg to 400 mcg, preferably 50 mcg to 200 mcg of selenium,

i. 0.9 mg to 300 mg, preferably 5 mg to 100 mg, of vitamin B1,

j. 1.5 mg to 400 mg, preferably 3 mg to 100 mg ofvitamin B6,

k. 200 mcg to 15 mg, preferably 1000 mcg to 10 mg of folic acid,

l. 1 mcg to 1000 mcg, preferably 10 mcg to 100 mcg of vitamin B12.

3. A process for the preparation of synergistic composition as claimed in claim 1 wherein, the said chromium is present in its pharmaceutically acceptable salts form like chroimum picolinate, chromium polynicotinate, chromium chloride, chromium-niacincomplex or the like.

4. A process for the preparation of synergistic composition as claimed in claim 1 wherein, the said zinc is present in its pharmaceutically acceptable salts form like zinc sulphate, zinc sulphate monohydrate, zinc gluconate, or the like.

5. A process for the preparation of synergistic composition as claimed in claim 1 wherein, the said selenium is present in its pharmaceutically acceptable salts from like selenium dioxide monohydrate, selenium methionine, or the like.

6. A process for the preparation of synergistic composition as claimed in claim 1 wherein other pharmaceutically acceptable excipients are selected from diluents like starch, microcrystalline cellulose, dicalcium phosphate, maltodextrin, or the like; adsorbent like silicon dioxide, magnesium aluminum silicate, microcrystalline cellulose or the like; binders like starch, gelatin, polyvinyl pyrrolidone, or the like; lubricants like talc, magnesium stearate, colloidal silicon dioxide, stearic acid, or the like; coloring agents; flavoring agents; flow-inducing agents and/or combination thereof.

7. A process for the preparation of synergistic composition as claimed in claim 1 wherein said oral dosage form can be in the form of tablet, dispersible tablet, chewable tablet, capsule, powder or granules filled in sachet packs or the like.

8. A process for the preparation of synergistic composition as claimed in claim 1 to 7 and substantially herein described and illustrated with examples.

Dated this 23rd day of October 2000

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